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Tissue-Specific Functions of the v-*myb* Oncogene

Leukemias are cancers of the blood, the uncontrolled outgrowth of cells which should be the normal components of our blood and/or lymph. The oncogenes are a class of genes, first discovered in the avian leukemia viruses, which can cause leukemias and other tumors because they interfere with the normal mechanisms for regulating cell growth. This project will study the properties of the *v-myb* oncogene, which can transform and cause the outgrowth of cells which lead to myeloid leukemias. Because *v-myb* encodes a transcription factor, a protein which binds to cellular genes and regulates their expression, it probably transforms cells and induces leukemias by altering the expression of genes which normally would control the growth and/or differentiation of the cells. One of the most interesting features about *v-myb* is that it only causes myeloid leukemias — it is unable to cause solid tumors or other kinds of leukemias. This may be because of some special feature of myeloid cells which the *v-myb* oncogene is able to take advantage of, something which makes such cells especially vulnerable to *v-myb*. We suspect that Myb requires the help of another myeloid-specific transcription factor to turn on *mim-1*. Indeed, the requirement for such a cofactor may be the reason that *v-myb* only causes myeloid leukemias. We have identified another transcription factor called NF-M which is only found in myeloid cells, and which is also required to activate the *mim-1* gene. We propose to study how the Myb and NF-M proteins interact with one another, for example, whether they form a complex. We have also recently found that introducing Myb and NF-M in other cells can cause myeloid genes to be turned on, effectively converting the cells, at least partially, to a myeloid phenotype. We will also test whether this phenomenon is generalized, and if it occurs in human leukemia cells. A better understanding of these processes will be crucial for determining how oncogenes like *v-myb* are able to induce leukemia, and why genes like *mim-1* are expressed in such tissue-specific ways.

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Screening for Tumor Suppressor Loci in a Transgenic Mouse Model of Lymphoma

Presently there is considerable evidence to suggest that genetic alterations play a significant role in leukemia and lymphoma. In most cases, however, the specific genes that are mutated in these tumors remain unknown. Recent studies have increasingly pointed to the importance of a class of oncogenes called tumor suppressor genes, whose inactivation results in loss of growth control and subsequent neoplastic transformation. I have developed a means to use a transgenic mouse model to test for regions of DNA that may be lost in tumors. Chromosomal regions that are consistently affected have been found in human tumors to contain tumor suppressor genes. Analysis of a mouse lymphoma model reveals the loss of the oncogene *p53* in several tumors. This demonstrates that it is feasible to use this approach for testing transgenic mouse lines which develop hematopoietic cell cancers for tumor suppressor genes that may be unique to these diseases. I propose to screen a large number of tumors from this transgenic line for additional loci that contribute to neoplastic transformation.